THE JOURNAL OF INVESTIGATIVE DERMATOLOGY, 63: 461–463, 1974

Vol. 63, No. 6
Printed in U.S.A.

EVALUATION OF ATROPHY PRODUCTION AND VASOCONSTRICTOR POTENCY IN HUMANS FOLLOWING INTRADERMALLY INJECTED CORTICOSTEROIDS*

DIANE SEKURA SNYDER, PH.D., AND ROBERT A. GREENBERG, M.D.

ABSTRACT

We have used intradermal injections of corticosteroids into normal and ultraviolet light (UVL)-induced inflamed human skin to evaluate the inherent atrophy-producing potential as well as the vasoconstrictor potency of selected compounds. Two corticosteroids, desonide and triamcinolone acetonide, which differ only by the presence of a fluorine atom, exhibited similar vasoconstrictor potency but only the fluorine-containing steroid produced severe, persistent atrophy. Hydrocortisone 17-valerate and desonide produced a mild, transient atrophy while hydrocortisone produced none. Triamcinolone acetonide and desonide were more effective than hydrocortisone and hydrocortisone 17-valerate in producing vasoconstriction in this model system of inflammation. The production of atrophy was always greater in the UVL-induced inflamed skin than in normal control skin.

Chronic usage of potent topical corticosteroids has been reported to cause atrophy, hypopigmentation, striae, and telangiectasia [1–3]. These side effects appear to be most severe in traumatized or inflamed skin [4]. It is not known whether the side effects are directly related to potency or fluorination of the corticosteroid. This study was undertaken to compare the inherent atrophy-producing potential of hydrocortisone with hydrocortisone 17-valerate, desonide (an acetonide derivative of 16-hydroxy prednisolone), and triamcinolone acetonide (a fluorinated derivative of desonide) in normal and ultraviolet light (UVL)-induced inflamed skin. These four steroids were also compared for their ability to cause vasoconstriction in skin inflamed by UVL. The corticosteroids were evaluated following a single intradermal injection.

MATERIALS AND METHODS

Corticosteroid powders were suspended in the following sterile medium for intradermal injection: 0.9 ml benzyl alcohol, 0.75 gm sodium carboxymethylcellulose, 0.04 ml Tween 80, 0.567 gm sodium chloride, and sufficient distilled water to make 100 ml. Steroid concentrations were 11.6 mM for hydrocortisone, and 5.8 mM for hydrocortisone 17-valerate, desonide, and triamcinolone acetonide.

Informed consent was obtained from the 13 healthy subjects (10 male and 3 female; aged 18 to 37) who participated in the study. Each subject received 2.5 minimum erythema doses of ultraviolet irradiation from a Westinghouse FS20 lamp to a rectangular area on the volar surface of the left forearm. One hour after the onset of redness 0.05 ml of each corticosteroid suspension (210 μg of hydrocortisone; 125 μg of the other steroids) and the suspending medium as a control were injected into the irradiated area and also into a corresponding site on the unirradiated right forearm in a double-blind fashion. The injection sites were separated from one another by at least 1.5 cm and each injection produced a distinct wheal with the characteristic "peau d'orange" appearance.

Grading of vasoconstriction. Blanching at the injection sites of the UVL-irradiated skin was evaluated at 2, 4, 24, 48, and 72 hr post injection. Blanch intensity (loss of redness) was graded according to the following qualitative scale; 0, no discernable blanch; 1, faint blanch; 2, obvious blanch; and 3, complete loss of UVL-induced redness with a blanch equivalent to the unirradiated normal skin. A grade 3 blanch is to be distinguished from loss of normal skin color, hypopigmentation, which was not fully appreciated in most subjects until 3 to 4 weeks after injection. The long diameter of the blanched site was measured in millimeters.

Grading of atrophy. The injection sites of both forearms were examined at 2, 3, 4, 6, 8, 12, 16, and 20 weeks. Dermal atrophy, a palpable depression in the skin, was graded on a scale of increasing intensity from 0 (no atrophy) to 4+ (severe atrophy).

Hypopigmentation, telangiectasia, and light yellow chalky deposits were noted when present and the injection sites of some subjects were examined with the aid of a dissecting microscope.

Data were analyzed for significance by analysis of variance and the nonparametric sign test [5].

RESULTS

Vasoconstrictor Potency

All 13 subjects demonstrated a decrease in UVL-induced redness over the sites of steroid injection in agreement with earlier observations [6]. Blanching was noted as early as 2 hr post injection. As can be seen in Figure 1, hydrocortisone and hydrocortisone 17-valerate demonstrated their maximal blanch intensity by 4 hr with respective mean blanch scores of 1.25 and 1.15. Triamcinolone acetonide and desonide caused greatest blanching at 24 hr with respective mean blanch scores of 2.4 and 2.1. By 48 hr the mean blanch intensity scores had decreased for all four steroids with hydrocortisone showing the greatest decrease. From 48 to 72 hr the mean blanch scores

Manuscript received May 20, 1974; in revised form July 19, 1974; accepted for publication July 22, 1974.

This work was supported in part by a grant from Westwood Pharmaceuticals and National Institutes of Health Grant T01 AM 05262 15.

* From the Department of Dermatology, University of Miami School of Medicine, Miami, Florida 33136.

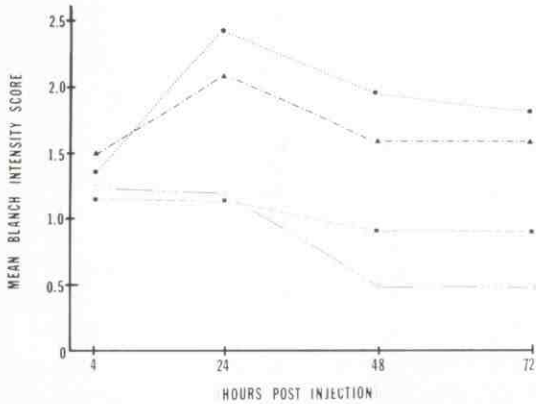

FIG. 1. Time course of corticosteroid-induced vasoconstriction following intradermal injection into UV-reddened skin. ---●--- = triamcinolone acetonide; ---▲--- = desonide; ---■--- = hydrocortisone 17-valerate; and ---○--- = hydrocortisone. The vehicle produced no blanching in this time period.

for all four steroids remained relatively constant. Both triamcinolone acetonide and desonide produced significantly more intense blanching than hydrocortisone and hydrocortisone 17-valerate at 24, 48, and 72 hr post injection ($p < 0.01$). Triamcinolone acetonide produced a higher blanch grade than desonide at the above times but these differences were not statistically significant. The differences in blanch scores between hydrocortisone and hydrocortisone 17-valerate were also not statistically significant.

The peak mean blanch diameters occurred at 4 hr for hydrocortisone (11.2 mm), triamcinolone acetonide (13.6 mm), desonide (11.5 mm), and hydrocortisone 17-valerate (10.4 mm).

Atrophy Production

Triamcinolone acetonide produced atrophy in all 13 subjects. Desonide and hydrocortisone 17-valerate produced atrophy in 9 subjects, while hydrocortisone produced no atrophy in any subject. In Figure 2 it is apparent that the atrophy produced by triamcinolone acetonide is more severe at every grading time than that produced by desonide and hydrocortisone 17-valerate. Atrophy over the sites of triamcinolone acetonide injection was noted in some cases as early as 1 week post injection. Maximal atrophy occurred in all subjects during the 4th week and persisted throughout the 8th week. By 20 weeks atrophy was present in only 2 subjects. The atrophy produced by desonide and hydrocortisone 17-valerate was relatively transient with a peak near the 4th week post injection. In only 1 subject did the atrophy persist beyond the 6th week. Mean atrophy scores for the irradiated sites were always greater than those for the unirradiated sites for the three steroids at every observation time.

Additional Side Effects

Triamcinolone acetonide caused hypopigmentation which persisted through the 8th week in all injection sites and through the 16th week for 7 of 13 subjects. Both desonide and hydrocortisone 17-valerate caused hypopigmentation in fewer subjects (9 of 13) than did triamcinolone acetonide. This hypopigmentation was apparent in only 2 subjects by the 12th week post injection. Hypopigmentation was not observed in the unirradiated injection sites until at least 2 weeks post injection. A decrease in tanning was seen in the UVL-irradiated sites as early as 4 days following injection. Hydrocortisone caused no hypopigmentation in any subject.

Seven subjects demonstrated the presence of light yellow chalky deposits at the triamcinolone acetonide injection sites as early as the 3rd week. Telangiectasia was noted in a different group of 7 subjects and appeared somewhat later than the chalky deposits (8 to 12 weeks). In 3 subjects, close examination with a dissecting microscope revealed decreased numbers of capillary loops in atrophic

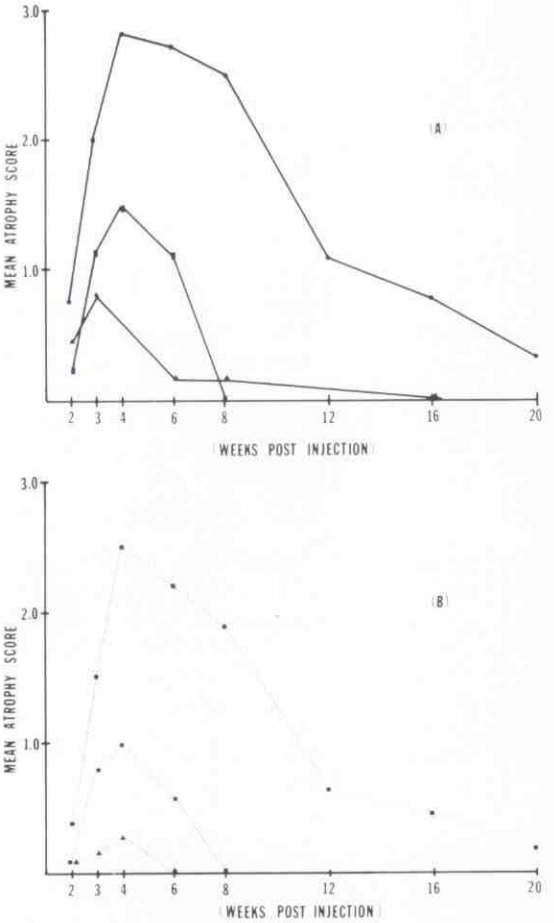

FIG. 2. Time course of corticosteroid-induced atrophy production following a single intradermal injection. ● = triamcinolone acetonide; ▲ = desonide; and ■ = hydrocortisone 17-valerate. Hydrocortisone and the vehicle produced no atrophy. *Top* shows the atrophy produced in UV-inflamed skin (solid lines). *Bottom* shows the atrophy produced in nonirradiated normal skin (dashed lines).

sites when compared to normal skin. Neither desonide, hydrocortisone 17-valerate, nor hydrocortisone produced telangiectasia or visible chalky deposits.

DISCUSSION

We have shown that a fluorinated prednisolone derivative (triamcinolone acetonide) and a nonfluorinated prednisolone derivative (desonide) are equally effective and greater than hydrocortisone and hydrocortisone 17-valerate in producing vasoconstriction in UVL-induced inflamed skin following intradermal injection but that only the fluorinated steroid causes significant long-lasting dermal atrophy. The lack of significant atrophy production by hydrocortisone 17-valerate is in agreement with Sneddon [7] who recently concluded that another ester of hydrocortisone, hydrocortisone 17-butyrate, is unlikely to cause atrophy. Any difference between triamcinolone acetonide and desonide in physiologic and physicochemical properties must be due to the presence of the 9-alpha-fluoro group in triamcinolone acetonide. Our data show that the addition of fluorine does not appear to significantly enhance the vasoconstrictor potency in inflamed skin in agreement with the findings of others [8] in normal skin. Several studies have reported a correlation between vasoconstrictor potency and anti-inflammatory activity of steroids [9, 10] although we are aware of no direct comparison between triamcinolone acetonide and desonide for therapeutic efficacy.

The presence of fluorine in the corticosteroid structure does correlate with the production of persistent atrophy, prolonged hypopigmentation, and telangiectasia. When a fluorine atom is introduced into the desonide molecule the resulting compound, triamcinolone acetonide, has only about ⅛ the aqueous solubility of desonide and hydrocortisone 17-valerate and ½ the aqueous solubility of hydrocortisone. This lessened solubility should be reflected in a longer residence time at the injection site. The more-water-soluble steroids would be more rapidly cleared from the local injection sites and thus would exert their action over a relatively shorter period of time. These differences in solubility may account for the varying degrees of atrophy which we have observed. Fluorine might also cause alteration in metabolism or interaction with the skin as is evidenced by the light yellow chalky deposits present only in the triamcinolone acetonide injected sites.

The mechanism of atrophy production has not been defined. Prolonged vasoconstriction might be expected to cause atrophy by decreasing the nutrient supply. Our data show that a period of vasoconstriction, up to 72 hr, is not sufficient to cause severe atrophy. The lower solubility and longer residence time of triamcinolone acetonide at the injection site could prolong vasoconstriction beyond 72 hr which might contribute to the decreased number of capillary loops we have observed along with other side effects. Corticosteroids can decrease the synthesis of collagen, acid mucopolysaccharides, and elastin by inhibiting the fibroblasts [11]. Since the beginning of atrophy was observed 1 week after injection in this study, this could be consistent with an early decrease in acid mucopolysaccharides as demonstrated histochemically [12]. An inhibition of collagen synthesis is unlikely to account for the apparent loss of tissue since the turnover time for collagen is very long, e.g., 1000 days in rats [13]. An increase in collagen breakdown cannot be ruled out since steroids have been reported to increase the activity of collagenase in rabbit cornea [14] and in rat skin [15].

REFERENCES

1. Epstein NN, Epstein WL, Epstein JH: Atrophic striae in patients with inguinal intertrigo pathogenesis. Arch Dermatol 87:450–455, 1963
2. Sneddon IB: Adverse effect of topical fluorinated corticosteroids in rosacea. Br Med J 1:671–673, 1969
3. Stevanovic DV: Corticosteroid-induced atrophy of the skin with telangiectasia. Br J Dermatol 87:548–556, 1972
4. Stankler L, Ewen SWB: The effects of corticosteroid injections at sites of skin damage. J Invest Dermatol 59:394–396, 1972
5. Cochran WG, Cox GM: Experimental Designs. Second edition. New York, Wiley, 1957, pp 103–116
6. Snyder DS, Eaglstein WH: Intradermal anti-prostaglandin agents and sunburn. J Invest Dermatol 62:47–50, 1974
7. Sneddon I: A trial of hydrocortisone butyrate in the treatment of rosacea and perioral dermatitis. Br J Dermatol 89:505–508, 1973
8. Stewart WD, Runikis JO, Verma SC, Wallace S: Problems in selection of topical anti-inflammatory corticosteroids. Can Med Assoc J 108:33–38, 1973
9. Reid J, Brookes DB: Topical corticosteroids—an experimental evaluation of the vasoconstrictor test as an index of anti-inflammatory activity. Br J Dermatol 80:328–336, 1968
10. Zaynoun ST, Kurban AK: Evaluation of the efficacy of topical corticosteroids. Br J Dermatol 90:85–90, 1974
11. Berliner DL, Ruhmann AG: Comparison of the growth of fibroblasts under the influence of 11 β-hydroxy and 11 keto corticosteroids. Endocrinology 78:373–382, 1966
12. Schetman D, Hambrick GW Jr, Wilson CE: Cutaneous changes following local injection of triamcinolone. Arch Dermatol 88:820–828, 1963
13. Thompson RC, Ballou JE: Studies of metabolic turnover with tritium as a tracer. IV. Metabolically inert lipids and protein fractions from the rat. J Biol Chem 208:883–888, 1954
14. Brown SJ, Weller CA, Vidrich AM: Effect of corticosteroids on corneal collagenase of rabbits. Am J Ophthalmol 70:744–747, 1970
15. Houck JC, Patel YM: Proposed model of action of corticosteroids on the connective tissue. Nature (Lond) 206:158–160, 1965